A case of SARS-CoV-2 reinfection in a patient with obstructive sleep apnea managed with telemedicine

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Accepted 17 January 2021

SUMMARY

The novel coronavirus (SARS-CoV-2) has produced millions of infections and deaths worldwide. It is believed that adaptive immunity to the virus occurs although with variation in its pattern and duration. While uncommon, confirmed reinfection with the novel coronavirus has been reported. Telemedicine has emerged as a viable tool for the delivery of healthcare in lieu of in-person patient contact. The variable and occasionally rapid course of clinical disease raises safety concerns of using telemedicine in the clinical management of acute infection with the novel coronavirus. We present a case of novel coronavirus infection in an immunocompetent individual with obstructive sleep apnea (OSA) who failed to manifest an adaptive immune response to acute infection and was subsequently reinfected. The case highlights the use of telemedicine in managing novel coronavirus respiratory disease and the potential role of OSA as a disease facilitator.

BACKGROUND

As of October 2020, the novel coronavirus pandemic has produced 39 million confirmed infections with an estimated 1 million deaths worldwide.[1] Reinfection with the novel coronavirus (SARS-CoV-2) may have widespread implications on clinical care. The Centers for Disease Control and Prevention (CDC) maintain that there is limited data on cases of reinfection in the USA.[2] The development and natural history of adaptive immunity to SARS-CoV-2 remains elusive as measurements of antibodies across individuals are inconsistent, with some experiencing waning of levels after 2–3 months, and uncommonly, some failing to generate antibodies.[3] Additionally, confirmed cases of repeat infection with SARS-CoV-2 vary in clinical presentation from mild to requiring hospitalisation, at times with greater symptomatology and derangement in gas exchange than the initial infection. Here, we report a case of acute symptomatic SARS-CoV-2 managed by telehealth who recovered without development of IgG antibodies and was reinfected, testing positive for SARS-CoV-2 infection via polymerase chain reaction (PCR) 11 weeks after the last negative PCR result.

CASE PRESENTATION

A 69-year-old white woman with a known history of mild intermittent asthma, hypercholesterolemia, hypertension and moderate obstructive sleep apnea (OSA) with documented adherence to positive airway pressure (PAP) therapy, was suspected to have infection with SARS-CoV-2 due to community exposure for which a nasopharyngeal swab PCR was performed on 6 April 2020. While pending the result of PCR, she developed shortness of breath, dry cough, headache, fatigue and subjective fevers. After evaluation by her PCP, she was empirically started on and completed a course of azithromycin and oseltamivir. A positive SARS-CoV-2 PCR prompted transition of care to her pulmonologist who employed daily telehealth (Zoom application supplemented by phone) and intermittent domiciliary assessment of oxyhemoglobin saturation by pulse oximetry (SpO_2) for surveillance of disease evolution. Room air SpO_2 levels in the low 90's at rest and 84%–87% with ambulation prompted recommendation for hospitalisation. The patient opted for continuation of outpatient management via telehealth. In the next several days, SpO_2 improved and cough and fatigued subsided. After 3 weeks, she tested negative for SARS-CoV-2 PCR on two nasopharyngeal swabs obtained 5 days apart. SARS-CoV-2 IgG serology assessed 12 weeks after the initial positive PCR was negative.

Approximately 10 weeks after testing negative for SARS-CoV-2 PCR, the patient presented to the emergency department with cough, fever and new-onset ageusia. SARS-CoV-2 nasal swab PCR was positive. She was discharged home to monitor symptoms with daily telehealth and SpO_2 monitoring. Symptoms worsened, room air SpO_2 deteriorated (88% at rest and 81% with ambulation) prompting hospitalisation.

While hospitalised, she received oxygen supplementation, remdesivir, dexamethasone, antibiotics and PAP while sleeping. She improved and was discharged home 7 days later with supplemental oxygen during ambulation.

Longitudinal care provided by telehealth and occasional in-person clinic visits document resolution of symptoms over the ensuing 3 months post discharge. SARS-CoV-2 PCR obtained 5 and 6 weeks after reinfection was negative. Ten weeks following reinfection SARS-CoV-2 serology was positive for IgG antibodies. Table 1 details the chronology and results of testing for SARS-CoV-2.

OUTCOME AND FOLLOW-UP

Follow-up in-person visits were conducted 6 and 9 weeks after the patient showed presence of antibody development by serology. Progressive improvement in condition was reported to her physician during intermittent telehealth follow-up. The patient

To cite:
Sicsic Jr I, Chacon AR, Zaw M, *et al*. *BMJ Case Rep* 2021;**14**:e240496. doi:10.1136/bcr-2020-240496

Table 1 Timeline and type of diagnostics performed

Date	Testing	Result
06 April	SARS-CoV-2 PCR	Detected
01 May	SARS-CoV-2 PCR	Not detected
06 May	SARS-CoV-2 PCR	Not detected
08 July	SARS-CoV-2 serology	Negative IgG
17 July	SARS-CoV-2 PCR	Detected
19 August	SARS-CoV-2 PCR	Not detected
25 August	SARS-CoV-2 PCR	Not detected
27 August	SARS-CoV-2 serology	Positive IgG
09 October	SARS-CoV-2 serology	Positive IgG

currently reports resolution of symptoms and continues to be positive airway pressure (PAP) compliant.

DISCUSSION

Recurrence of positive SARS-CoV-2 PCR after initial clinical recovery and negative SARS-CoV-2 PCR after acute infection has been previously reported. Yuan *et al* described 172 patients discharged from the hospital after clinical recovery and two times negative for SARS-CoV-2 PCR separated by 24 hours. Domiciliary follow-up with nasopharyngeal and cloacal SARS-CoV-2 PCR every 3 days returned newly positive results on 25 (14.5%). The average time (days±SD) between the last positive PCR and newly positive PCR was 7.32±3.86. The majority of these cases converted to PCR positivity without aggravation of symptoms and worsening of thoracic imaging.[4] The Korea Centers for Disease Control and Prevention reported on 285 out of 447 individuals who tested SARS-CoV-2 PCR positive a second time after being discharged from isolation and described the average time lapsed was 14.3 days. Depending on geography and groups (all, school staff, students, nursing home) 25.9%–48.9% of cases tested positive again after discharge.[5] Similarly, two cases of acute SARS-CoV-2 PCR-positive pneumonia with documented improvement of acute infection and negative SARS-CoV-2 PCR before discharge required hospital readmission for respiratory symptoms and repeat SARS-CoV-2-positive PCR 14 and 16 days after discharge from the initial hospitalisation.[6 7] Such cases may represent prolonged shedding or false-negative SARS-CoV-2 PCR as opposed to true reinfections.[8] However, recurrence of symptoms in some with repeat positive SARS-CoV-2 is suggestive of reactivation and/or repeat infection.

Comparable to the temporal profile of our patient's disease process, a report by Van Elslande *et al*[9] describes a woman in Belgium who initially presented with symptoms of SARS-CoV-2 infection confirmed by nasopharyngeal swab. Antibody testing was not conducted at the time. She was home quarantined for 5 weeks, but relapsed 3 months after first infection, although describing milder symptoms. On resolution of symptoms, serology showed presence of the adaptive immune response and the genomic analysis showed differing lineages of SARS-CoV-2 between the first and second occurrences, a finding that favours repeat infection.[9]

More recently, reinfection was accompanied with a worse clinical course. Three patients who recovered from first infection sought medical attention with severe symptoms at the time of reinfection after 6, 8 and 10 weeks.[10–12] All three cases reported high levels of SARS-CoV-2-specific antibodies after the second infection. However, none of the cases reported SARS-CoV-2 antibody testing after the initial infection.

Xiang *et al*[13] studying antibody dynamics reported that IgM and IgG antibodies were detectable 4 days after symptom onset. Further, a study by Xiao *et al*[14] that conducted serial monitoring of patients with confirmed SARS-CoV-2 infection showed the development of IgG in all patients after 7 weeks. Evidence of the development of adaptive immunity was later appreciated in our patient 6 weeks after reemergence of symptoms.

Technical limitations inherent in SARS-CoV-2 testing can confound the interpretation of findings in our case.[15 16] Of the few publications discussing the reliability and validity of reverse transcription (RT)-PCR for SARS-CoV-2, Katz *et al*,[17] mention a specificity between 63% and 78%. According to Sethuraman *et al*,[16] however, antibody testing that is ELISA-based have specificities above 95% in the diagnosis of SARS-CoV-2, highlighting its usefulness in diagnosing SARS-CoV-2. RT-PCR and antibody testing for SARS-CoV-2 have proven to be invaluable and necessary in the diagnosis and management of SARS-CoV-2.

Whether long-standing immunity after acute SARS-CoV-2 occurs remains uncertain. Patel *et al* described a reduction in antibody seropositivity over 60 days with 58% of initially seropositive individuals becoming seronegative.[18] Thus far, reinfection with SARS-CoV-2 reportedly occurs around 2 months after the initial infection. Our case developed recurrence of symptoms at 3 months, perhaps owing to a less robust initial immune response. That some have a worse clinical presentation at the time of second infection has been reported by others.[10–12] Clinical severity may be linked to the magnitude of the immune response as was suggested by Long *et al*[3] and Stephens and McElrath.[19]

Our case presented with greater severity of clinical symptoms on second infection. The observation argues against prolonged shedding.[4–12] Also, it can potentially be attributed to a new strain of coronavirus associated with differing virulence factors as described by Goldman *et al* who detected a spike variant D614G 140 days after initial infection.[8] Alternatively, a pathophysiological response similar to dengue fever wherein a previous exposure with viruses 1–4, enhances viral replication in vitro and causes severe disease in animal models, or in the case of a different strain of the virus, may lead to 'antibody-dependent enhancement'.[20] In either circumstance, the clinical presentation is accentuated by one's immune response.

Recent studies suggest that there is an increased risk of SARS-CoV-2 infection severity in patients with OSA who become infected, citing that proper treatment of OSA may be beneficial in mitigating the acuity of illness.[21] Nocturnal hypoxaemia and sleep fragmentation, both common to OSA, have been linked with inflammatory processes similar to SARS-CoV-2-related acute respiratory distress syndrome.[22 23] In the Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study, patients identified as OSA on treatment before hospital admission for SARS-CoV-2 had a higher risk of mortality.[24] Based on these findings, our patient was at risk for severe disease from SARS-CoV-2. However, our patient was PAP adherent pre-SARS-CoV-2 and mean nightly PAP use increased from preinfection by 20.8%–21.9% following the first and second bout of infection, respectively. The increase in PAP usage can be attributed to the frequent telehealth visits with remote monitoring of PAP use. Additionally, the patient had increased in sleep duration after each infection, which could potentially improve adaptive immunity.[25]

Prior to the pandemic, the concept of healthcare delivery via telemedicine was largely ignored.[26] The pandemic necessitated widespread adoption and utilisation of telemedicine. Recent findings estimate that older adults are more likely to be accepting of

video visits compared with 2 years ago.[27] Reflecting a readiness to embrace this mode of healthcare delivery, our case frequently exploited telemedicine. In this case, the use of telemedicine, at least initially, decreased resource utilisation and contagion risk from acute SARS-CoV-2.

Loss of antibodies with time postacute SARS-CoV-2 infection and the possibility of 'antibody-dependent enhancement' may affect therapeutic responses. The former by reducing SARS-CoV-2 antibody levels acquired via infection or plasma infusion, and the latter if antibody-enhanced SAR-CoV-2 disease occurs similar to dengue.[18–20 28]

The duration of the protection conferred by natural immunity to SARS-CoV-2 remains a subject of scientific investigation.[29] In the USA, the CDC advocates to delay offering the vaccine to individuals with prior SARS-CoV-2 infection until 90 days have elapsed following the acute infection.[30] The recommendation is based largely on data from human coronavirus NL63.[31] Surveillance following SARS-CoV-2 vaccination will inform future health policy on SARS-CoV-2 vaccines.

CONCLUSION

The natural history of reinfection by SARS-CoV-2 and its immune response needs to be better characterised as its variability and pathophysiologic mechanism impact management. Reinfection with SARS-CoV-2 is uncommon but within the realm of possibility mandating heightened awareness by clinicians. This case highlights complexity of managing SARS-CoV-2 and illustrates the value of telemedicine which, in allowing distant regular surveillance and healthcare, facilitated effective allocation of resources and minimised contagion risk.

Learning points

- As cases of reinfection begin to be described more frequently, the reinforcement of social and hygienic practices to prevent occurrence takes greater relevance.
- Telemedicine is a valuable tool for medical surveillance in the management of novel coronavirus infection as it decreases contagion exposure in healthy individuals, and spread of infected patients.
- Adherence to comorbidities treatments as in the case of obstructive apnea may mitigate the effects of novel coronavirus infection.

Contributors ISJ performed the initial literature review, obtained consent and wrote the initial draft of the manuscript. ARC provided the general framework, performed extensive editing, revisions and expanded on the manuscript's content. MZ conducted further literature review, edited the case presentation and augmented content in the discussion. ARA identified the patient's case as being a potential report, conceived the clinical lessons, diagnosed the case, treated and followed up on the patient as the attending physician. KA reviewed and added key concepts for discussion of the case. ADC comprehensively reviewed and revised the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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